FDA Clinical Review of

BLA 98-0369

Herceptin®
Trastuzumab
(rhuMAb HER2)

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Sponsor: Genentech, Inc.

Food and Drug Administration
Center for Biologics Evaluation and Research

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Portions of the reviews of the statistical, product and pharmacology/toxicology sections have been included in the clinical review in order to improve the logical flow of the content and provide the reader with a comprehensive overview of the subject.

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1.0 BACKGROUND OF THE PRODUCT - HERCEPTIN®

1.1 Introduction

Breast cancer is one of the most common malignancies in women. It accounts for approximately 1/3 of female cancer in the USA and therefore, remains a serious health care problem. Approximately 25-30% of breast and ovarian cancers overexpress HER2/neu. Abnormal expression of the HER2/neu is frequently observed in a number of primary tumors, suggesting that overexpression may contribute to transformation and tumorigenesis. HER2/neu overexpression has been correlated with poor clinical outcome in patients with breast and ovarian cancers. HER2/neu overexpression appears to be associated with shorter disease-free interval, shorter overall survival, more rapid disease progression (higher incidence of metastasis), and resistance to chemotherapy in retrospective studies.

1.2 Herceptin®

Herceptin® (trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that targets the extracellular domain of the ErbB-2/Her2/neu receptor. It was engineered by grafting the complementarity determining regions of the parental murine antibody (4D5) into the consensus framework of a human IgG1.

Herceptin® has been produced from CHO cells maintained in cell culture systems at Genentech for human clinical trials since 1991. The entire cell culture process from Master Cell Bank through final production contains no serum or other animal proteins.

1.2.1 BACKGROUND

The HER2 Receptor

The human epidermal growth factor receptor 2 (ErbB-2/ HER2^{p185}) is a member of Type I family of growth factor tyrosine kinase receptors. The family also includes the endothelial growth factor receptor (EGFR), HER3, and HER4 receptors. These receptors are encoded by homeotic genes and share extensive sequence homology, suggesting a similar mechanism of activation and signaling. These receptors function by forming hetero- and homo-dimers with members of the family.

The c-ErbB-2/ HER2^{p185} proto-oncogene encodes a 185 Kd trans-membrane glycoprotein that participates in an interactive network of receptor-receptor interactions. These interactions regulate cell fate, growth and proliferation, mainly through MAP and Kinases.

Current data indicate that HER2 acts as co-receptor or a shared signaling sub-unit, prolonging and enhancing activation of proteins involved in signal transduction pathways

Normal Expression of Her2^{p185} and Its Role in Embryogenesis:

Immunohistochemistry staining showed that HER2/neu is normally widely expressed in differentiated adult and in fetal tissues derived from the three embryonic germ layers. High intensity staining was reported in the gastrointestinal tract (Press M. et al. Oncogene 1990) and the proximal tubules and loop of Henle of the urinary tract (Gullick W. et al. Int. J. Cancer, 40:246-254 (1987).

Recent studies (Lee K. et al. Nature 378:394-396, 1995) demonstrated that expression of HER2/neu is crucial for cardiac and CNS development. Mice carrying the null allele died at E11 due to the lack of cardiac trabeculae formation. The development of cranial neural-crest derived sensory ganglia as well as the motor nerves, was also compromised. (Lee K. et al. Nature 378:394-396 (1995).

Role of HER2^{p185} in Signal Transduction

The current literature supports a normal role for HER2/neu as the preferred partner of all the other family members (Karunagaran D. et al. Embo J:15: 254-264). Several ligands have been characterized that bind the EGFR, HER3 and HER4. EGF and transforming growth factor-alpha (TGF-alpha) are among the ligands for EGFR, and heregulin/NDF (neu differentiation factor) is the ligand for HER3 and HER4. No specific ligand for HER2 has been found.

Ligand binding to the respective receptors induces a conformational change of the receptor, which in turn results in a) tyrosine autophosphorylation and b) increased binding affinity for the other receptors.

The increased binding affinity results in hetero/homodimer formation. As a result of ligand binding, the intracellular tyrosine kinases become activated and transphosphorylate the binding partner (e.g., HER2^{p185}). These events initiate the signal transduction pathway. The ultimate step in all Erb family members' activation is mitogenesis.

HER 2^{p185} Overexpression

In humans, the oncogenic transformation of HER2/neu has invariably correlated with protein overexpression. Due to its constitutive kinase activity, HER2/neu overexpression results in enhanced tyrosine phosphorylation activities. Constitutive tyrosine kinase activity leads to increased proliferation rate, resistance to TNFa, decreased expression of adhesion molecules (E-cadherines and integrins) and increased vascular endothelial growth factor (VEGF) secretion.

Mechanism of action of Herceptin®

Herceptin® acts *in vitro* by a dual mechanisms of action:

a) Biochemical: Exerted by binding to the HER2^{p185} receptor.

Herceptin binding to $HER2^{p185}$ blocks dimer formation and induces down-regulation of the receptor. Both events lead to the blockade of the signal transduction pathway.
In addition, Herceptin has the following *in vitro* effects:

- Cytostasis: inhibition of proliferation by interference with the mitogenic activity of the HER2/neu receptor due to the induction of the CDK2 kinase inhibitor, $p27^{KIP1}$ and the retinoblastoma-related protein, p130;
- Reduction of the cellular resistance to TNFa;
- Restoration of the expression of adhesion molecules (E-cadherines, a2 integrins) involved in metastasis development and progression,
- Reduction of VEGF production

b) Immunological: Exerted by Fc binding to the FcgRIII of CD16+ cells.
In vitro studies demonstrated that Herceptin®, in the presence of PBMN, was able to mediate ADCC (antibody-dependent cell-mediated cytotoxicity). This effect was due to binding of the MAb to the FcgRIII present on the surface of cytotoxic cells (NK, CD8+ T cells, monocytes, macrophages, and activated PMN). It is postulated that in the *in vivo* setting, Herceptin® may recruit immune cells to the tumor site.

2.0 SPONSOR'S PROPOSED INDICATION

Genentech, Inc. proposed that Herceptin® be approved for the following indication(s):

"Herceptin® is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2."

3.0 Clinical Pharmacology Review of Herceptin®

Herceptin® is a recombinant humanized monoclonal antibody (MoAb) that selectively targets HER2/neu, the extracellular domain of the EGF receptor 2 protein. The MoAb is an IgG1 that contains human framework regions with the CDR of a murine antibody that binds to HER2/neu. Herceptin® binds with high affinity to the HER2/neu protein, inhibits proliferation of human tumor cells that overexpresses HER2/neu in vitro and in vivo, and is a potent mediator of ADCC.

Clinical pharmacokinetics were studied in three Phase 1, three Phase 2, and one Phase 3 investigations in patients with metastatic breast cancer with tumors that over express the HER2/neu gene product. Both single dose and multiple dose kinetics were studied. Pharmacokinetic data were collected as part of clinical safety and efficacy trials and no clinical studies were conducted to specifically investigate special populations, pharmacokinetics profiles or formulation issues.

From data used to perform a pharmacokinetics stimulation analysis, a weekly dose of 100 mg was selected for study and found to provide trough levels within the serum levels thought efficacious (10 to 20 μg/ml based on preclinical studies). A loading dose of 250 mg was added to the dosing regimen to attain the target levels more quickly. Experience in early clinical development suggested that rather than administer a fixed dose of 250 and 100 mg, a body weight adjusted dose of 4 mg/kg as a loading dose and 2 mg/kg as a maintenance dose would improve the consistency of response. Furthermore, a minimum target trough level of 20 μg/ml was selected as the lower limit of serum levels to be maintained upon repeated dosing.

Although the mechanisms of Herceptin® clearance are not specifically established, the presence of shed antigen from the HER2/neu receptor is known to increase the clearance of Herceptin®.

The following studies investigated the pharmacokinetics of Herceptin®:

Phase 1 studies

1. H0407g: a single dose study of 10, 50, 100, 250, and 500 mg

2. H0452g: a multi-dose once weekly dosing regimen of 10, 50, 100, 250, or 500 mg

3. H0453g: a multi-dose once weekly dosing regimen of 10, 50, 100, 250 or 500 mg with cisplatin

Phase 2 studies

4. H0551g: multi-dose given once weekly dosing regimen of 250 mg loading dose and

100 mg maintenance dose

5. H0552g multi-dose given once weekly dosing regimen of 250 mg loading dose and 100 mg maintenance dose with cisplatin

Phase 3 studies

6. H0648g once weekly multi-dose study of 4 mg/kg loading dose and 2 mg/kg maintenance dose in patients given Herceptin® and chemotherapy

7. H0649g once weekly multi-dose study of 4 mg/kg loading dose and 2 mg/kg maintenance dose in patients given Herceptin®

Summary of Pharmacokinetics:

Single dose studies were conducted in Phase 1 and used to characterized the pharmacokinetic profile of the MoAb. In multi-dose studies conducted in Phase 2, only trough and peak samples were obtained. Peak samples were collected within 1-hour of the end of Herceptin® infusion. In addition to quantifying levels of Herceptin®, all serum samples were also analyzed for shed antigen and antibodies to Herceptin®. In one Phase 2 study and one Phase 3 study, shed antigen was determined at various times which included pretreatment samples.

For serum levels of Herceptin®, pharmacokinetic data were fit to either a 1 or 2 compartment model as determined by the best fit of the data to the regression line. AUC, Cl and Css (steady-state concentrations) were determined using non-compartmental methods. Trough and peak serum levels were observed samples without modification. Half-life was determined by a standard technique using the slope of the terminal elimination phase.

Various factors were found to modify the pharmacokinetics of Herceptin® including dose and shed antigen. Early studies demonstrated that Herceptin® clearance (Clt) decreased with increasing dose as shown in the tables below. Concomitantly, half-life (t1/2) increased with decreases in Clt following increased dosage. Since the volume of distribution remained basically unchanged with increases in dose, it is likely that the changes in Clt and t1/2 reflect an alteration in the elimination pathways of the MoAb rather than the extent of distribution. However, steady state serum levels were found to rise upon repeated dosing without an observable change in clearance suggesting that later rises in serum levels which occurred with repeated dosing may be due to alterations in distribution rather than elimination.

Additionally, Phase 1 studies revealed that an increased clearance of Herceptin® correlated with levels of shed antigen in patients. The association between shed antigen and Herceptin clearance was found to be continuous rather than a step function with a specific cutoff such as 500 ng/ml. Given the dose selected for Phase 3 and the rise in

trough levels of Herceptin® with repeated dosing, only about 9% of patients failed to achieve a level of 20 µg/ml of Herceptin® in a Phase 3 study. The percentage of patients with shed antigen levels >500 ng/ml varied in the different studies between 0 and 24%. The highest percentage was observed in study H0452g and the lowest percentage in study H0453g. The Phase 2 study H0649g demonstrated an elevated shed antigen level in 6.3% of the patients.

Ninety-one per cent (177/195) of the patients given a maintenance dose of 2 mg/kg obtained a trough serum level of 20 µg/ml or higher at one or more sampling times as observed in H0649g over the first 8 weeks. Trough serum concentrations at week 8 in studies H0648g and H0649g were greater than predicted from simulations based on Phase 2 data which suggests that later changes occur in the pharmacokinetics of Herceptin® upon repeated dosing. Serum concentrations achieved an observed steady-state level later (12 to 32 weeks) than would be predicted by their earlier pharmacokinetics (at approximately 4 weeks) due to unknown factors.

Serum levels were not found to be indicative of outcome in the clinical study, but any relationship of pharmacokinetics to patient outcome is likely confounded by several clinical factors such as disease burden and prior chemotherapy. No data are available regarding the possible relation between tumor burden, shed antigen and pharmacokinetics of Herceptin.

No formal clinical drug-drug interaction studies were conducted to investigate the potential influences between the pharmacokinetics of Herceptin® and cisplatin, doxorubicin or epirubicin plus cyclophosphamide or paclitaxel. A comparison of serum levels of Herceptin® given in combination with various chemotherapeutic agents did not suggest the possibility of any interactions except in combination with paclitaxel. Although not statistically significant, mean serum trough concentrations of Herceptin® in combination with paclitaxel were observed to be consistently elevated when compared to serum of Herceptin® levels when combined with AC. A non-clinical study in primates suggests that although the combination Herceptin® with doxorubicin and cyclophosphamide does not effect the pharmacokinetics of Herceptin® or the chemotherapeutic agents, the pharmacokinetics of Herceptin® are altered by paclitaxel. Clearance of Herceptin® was statistically decreased when administered with paclitaxel. In the monkeys given Herceptin® alone, clearance was 0.85± 0.054 ml/hr/kg, whereas in the paclitaxel treated group it was 0.48± 0.09 (X ± SD). The non-clinical study used a different dosing regimen than that used clinically as the non-clinical study used an iv bolus administration of Herceptin® followed by a 60 minute iv infusion. No effect on paclitaxel pharmacokinetics were observed in combination with Herceptin® in monkeys.

Based on clinical and non-clinical studies, changes in formulation did not influence the pharmacokinetics of Herceptin®. Changing from a single-dose liquid to multiple-dose lyophilized formulation did not appear to change the pharmacokinetics of Herceptin® as Cmax and AUC were found to be similar in patients given either formulation in a Phase 3

study (H0648g). Additional evidence for a lack of effect on the pharmacokinetics of Herceptin® with changes in formulation or manufacturing was demonstrated in a series of non-clinical studies which were conducted using rhesus monkeys. These studies revealed no changes in pharmacokinetics incident to single dose vs multi-dose preparations, changes in the cell line used or scale-up for manufacturing purposes.

Tables which summarize the pharmacokinetics of Herceptin follow:

Dose, mg (mg/kg)	N	t1/2, hr (days)	Clt, ml/d/kg	Vd, ml/kg
10 (0.167)	9	36 (1.5)	26.5	53.6
50 (0.802)	9	103 (4.3)	10.3	51.5
100 (1.58)	9	155 (6.5)	7.5	55.3
250 (3.37)	10	242 (10.1)	5.72	48.5
500 (8.05)	11	373 (15.5)	5	65.6

Table of Summary of Pharmacokinetic Endpoints for Herceptin as a 90 Minute iv Infusion Across Studies H0452g, H0407g and H0453.

Dose, mg	N	t1/2, hr (days)	Clt, ml/d/kg	Vd, ml/kg	*Ctrough*, ug/ml	*Cpeak*, ug/ml	*Css*, ug/ml
250/100	82	218 (9.1)	6.2	51	18.3	117	102

Table of Summary of Pharmacokinetic Endpoints for Herceptin given as 250 mg Loading Dose plus a 100 mg Maintenance Dose (once weekly) Given in Studies H0551g and H0552g. *Ctrough*, *Cpeak*, *Css* were averaged across all observations.

Dose, mg/kg	N	t1/2, hr (d)	Clt, ml/d/kg	Vd, ml/kg	*Ctrough*	*Cpeak*	*Css*
4/2	159	141 (5.9)	5.08	36.3	53.6	99.8	55.6

Summary of the Pharmacokinetics of Herceptin® Averaged from Studies H0648g and H0649g. Study H0648 examined the effects of concomitant chemotherapy: doxorubicin or epirubicin plus cyclophosphamide or paclitaxel. *Ctrough*, *Cpeak*, *Css* were observed at week 8 of repeated dosing.

The potential contribution of paclitaxel to augment serum levels of Herceptin® in comparison to other chemotherapeutic agents, suggests caution in generalizing any clinical benefit across a variety of chemotherapeutic agents.

Please see Appendix B for details of the pre-clinical pharmacology/toxicology review.

4.0 METHODOLOGY OF THE CLINICAL REVIEW - OVERVIEW

4.1 Clinical Studies

This Biologics License Application (BLA) for Herceptin® was granted priority review status and fast track designation; the sponsor was permitted to submit the contents in a rolling fashion with a complete application filed on May 4, 1998. Additional items have been submitted since that time. Some of these were planned (efficacy and safety updates) and some were responses to the requests of the FDA reviewers. The efficacy SAS data sets were updated at the end of May 1998. The safety data update was received in mid July 1998. A major efficacy update was received from the sponsor at the end of August 1998. Requested imaging studies were received in mid September 1998.

The following is a tabular summary of the studies conducted under IND 4517 and which have been submitted to the BLA. Case Report Forms were submitted for studies H0648g and H0649g only.

Studies submitted to the BLA:

Study # Phase	Regimen	#pts	Indication	Accrual Status
H0407g Phase 1	Single dose 10, 50, 100, 250, 500 mg	n=16	met. cancer Her2 (1-3+)	closed
H0452g Phase 1	Weekly dosing 10, 50, 100, 250, 500 mg plus MTP[a]	n=17	met. cancer Her2 (1-3+)	closed
H0453g Phase 1	Weekly dosing 10, 50, 100, 250, 500 mg Plus Cisplatin 100 mg/m2 plus MTP[a]	n=15	met. cancer Her2 (1-3+)	closed
H0551g Phase 2	Weekly dosing 250 mg load/100mg weekly plus MTP[a]	n=46	met. breast ca. Her2 (2-3+)	closed
H0552g Phase 2	Weekly dosing 250 mg load/100mg weekly Plus Cisplatin 75 mg/m2 plus MTP[a]	n=39	met. breast ca Her2 (2-3+)	closed
H0648g Phase 3 Pivotal Study	*Weekly dosing* *4 mg/kg load 2 mg/kg weekly* *Plus AC or Paclitaxel vs chemo alone* *May go to H0659g at PD*	*n=469*	*met. breast ca* *Her2 (2-3+)*	*closed*
H0649g Phase 2	Weekly dosing 4 mg/kg load 2 mg/kg weekly Plus at PD 2 or 4 mg/kg ± chemo	n=222	met. breast ca Her2 (2-3+)	closed
H0650g Phase 2	Weekly dosing 4 mg/kg load 2 mg/kg weekly or 8 mg/kg load 4 mg/kg weekly	n=62	met. breast ca Her2 (2-3+)	ongoing
H0659g Phase 2	Weekly dosing 4 mg/kg load 2 mg/kg weekly ± antitumor therapy	n=157	met. breast ca Her2 (2-3+)	ongoing
H0693g Phase 2	Weekly dosing 4 mg/kg load 2 mg/kg weekly ± antitumor therapy	n=163	met. breast ca Her2 (any test)	ongoing

a MTP refers to a Maintenance Treatment Program which allowed the patient to continue to receive Herceptin® weekly until progressive disease.

4.2 Analyses

Most analyses were conducted using the SAS data sets submitted by the sponsor. In particular instances where the FDA chose to perform intensive review of the raw data in the CRF's and patient narratives, the information was entered into separate FDA generated data sets from which analyses were performed. This was performed for selected adverse events (cardiac, hematologic, infectious, hospitalizations, pain, growth factor use, transfusions), determination of sites of disease (visceral, superficial (soft tissue) or bone), reasons for discontinuation of therapy, and determination of tumor response and time to progression. In addition, original imaging studies (e.g. CXR's, CT scans, bone scans) of some patients were reviewed by the FDA. Instances where the FDA based analyses were performed are clearly noted in this document.

Response Evaluation Committee (REC)

The REC was established in December 1996 after the protocols had been underway for over one and a half years. It was a blinded committee (blinded to study and blinded to treatment arm) with a separate charter which outlined procedures for acquisition of films from the sites, maintaining uniform criteria for determining response, and contacting the sites with results in a timely fashion. The committee was composed of 8 oncologists and 10 radiologists. Each reading team consisted of one oncologist and one radiologist. Internal validation studies were conducted to ensure that inter-reader variability was > 80% with a goal of 90%; we have not reviewed these inter-reader variability data. The readings occurred every 2 weeks and investigators were notified of the results by fax. The charter outlined in great detail what imaging studies were required, how frequently they should have been performed, and what other ancillary data, such as pathology reports, should have been submitted to the REC. Since the tumor measurements obtained by the site investigators were not collected on the CRFs, the REC evaluation was the only tumor measurement data available for review. All patients were to be reviewed by the REC.

Some elements of the REC charter, however, were problematic:

a) The charter did not allow the REC to consider effusions (pleural effusions, ascites) as malignant unless there was cytopathologic evidence of malignancy.
b) The charter did not allow the REC to consider new lesions on bone scans (either initial or sequentially increasing in number) as malignant unless there was a CT, MRI or plain X-ray confirmation.
c) While the charter did require that the REC evaluate all sites of disease and all imaging studies, it did not require the REC to comment on other than the indicator lesions selected; for example, there may be a progressive increase in the size of a pleural effusion on sequential films, yet the data conveyed on the REC CRF's did not indicate this finding.

Because of the problems in the charter, imaging studies of approximately 4% of the patients enrolled on studies H0648g and H0649g were reviewed by the FDA. The conclusion of this film review was that, in general, the REC analysis was rigorous and in many cases conservative. In a small number of cases which fell into the problematic areas noted above, the FDA analysis differed with the REC analysis and in those cases the FDA analysis was used in calculating the endpoints.

4.3 Validation

Particular attention was placed upon validation of chemotherapy treatment and Herceptin® treatment. Herceptin treatment validation was complicated by the fact that the study began as a placebo controlled study and then was amended to become an open label trial; some patients who enrolled when the placebo therapy was in effect had vial lot numbers entered on their case report forms and some did not. The sponsor was asked and has supplied the codes for the blind and copies of the returned vial labels from those patients for whom no lot number was entered on the case report forms. Throughout the review process consistency between CRF entries and SAS data sets was examined.

4.4 Status of the Clinical Review

This review is based primarily on data submitted for studies H0648g and H0649g. These are the only studies for which CRFs have been submitted.

5.0 CLINICAL TRIAL H0649g - PHASE 2, SINGLE ARM STUDY

5.1 Title H0649g

A Multinational, Open-Label Study of Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) in Patients with HER2/neu Overexpression Who Have Relapsed Following One or Two Cytotoxic Chemotherapy Regimens for Metastatic Breast Cancer

Conducted April 24, 1995 to June 4, 1997

5.2 Study design and conduct H0649g

5.2.1 Objectives H0649g

Primary endpoints of this study were the overall response rate defined as the sum of the complete and partial responses and delineation of the safety profile of Herceptin® as a single agent in patients with metastatic breast cancer.

Secondary endpoints were the duration of response, time to progression, time to treatment failure, survival, and quality of life. Please refer to Appendix D for all definitions.

5.2.2 Design H0649g

This is a Phase 2, open label, single arm study of Herceptin® conducted at 54 centers in the North America, Europe, and Australia/New Zealand. The target enrollment was 200 patients.

5.2.3 Patient Selection H0649g

The selection criteria for patients was amended in May 1996. Below is a list of the criteria from the original protocol and in its amended format.

Table 1. Selection criteria H0649g

Selection criteria	Original protocol - April 1995	Final protocol - May 1996
Age	18 or older	18 or older
Diagnosis	Metastatic Breast Cancer	Metastatic Breast Cancer
Prior chemotherapy for breast cancer	Progression following two regimens for metastatic disease or one regimen if relapsed with metastases less than a year following adjuvant therapy or if received high dose consolidation regimen in the adjuvant setting and one prior regimen for metastatic disease	Progression following one or two regimens for metastatic disease.
Bilateral breast cancer	Acceptable only if both primary tumors are 2+ or 3+ or all metastatic sites are 2+ or 3+ for HER2 by IHC	Acceptable only if both primary tumors are 2+ or 3+ or all metastatic sites are 2+ or 3+ for HER2 by IHC
HER2 positivity of tumor	2+ or 3+ by immunohistochemistry	2+ or 3+ by immunohistochemistry or FISH
Life expectancy	> 3 months	eliminated
Measurable disease	Mass at least 1 cm in greatest dimension measurable in 2 dimensions by physical , CT, MRI, ultrasound, or photos.	Mass at least 1 cm in greatest dimension measurable in 2 dimensions by physical , CT, MRI, ultrasound, or photos.
Karnofsky performance status	60% or better	60% or better
Creatinine	<1.7	eliminated
Bilirubin	<2.5	eliminated
White blood cell count	> 3000	eliminated
Platelet count	> 80,000	eliminated
Hemoglobin	> 8.5	eliminated
Calcium	< 11.0	eliminated
Radiation therapy	Completed greater than 2 weeks prior to entry	eliminated
Hormonal therapy	Stopped more than 2 weeks prior to entry	eliminated
Brain metastases	Not allowed	Allowed if stable after radiation treatment
Investigational agents	Stopped therapy more than 30 days prior to entry	Stopped therapy more than 30 days prior to entry

5.2.4 Treatment H0649g

Herceptin® was administered as an intravenous infusion in the outpatient setting. The initial loading dose was 4 mg/kg infused over 90 minutes with a one hour observation period. If the first dose was well tolerated all subsequent infusions were administered weekly at a dose of 2 mg/kg infused over 30 minutes with a 30 minute observation period for the second dose and no observation thereafter. If the initial or maintenance infusions were not well tolerated then all subsequent infusions were infused over 90 minutes. Doses were to be adjusted for changes in the patient weight, but no dose reductions were designated for adverse events; a dose was either administered or held.

After a patient was found to have progressive disease, she had the following options:

a) discontinue from the study
b) continue on with Herceptin® at 2 mg/kg weekly with or without chemotherapy or hormonal therapy
c) continue on with Herceptin® at 4 mg/kg weekly with or without chemotherapy or hormonal therapy

5.2.5 Concomitant therapy H0649g

Radiation therapy to localized sites of disease could be administered to patients if medically necessary during the study provided the sites which were irradiated were not used by the investigator to evaluate tumor response.

Chemotherapy could be added at the time of progressive disease (see above).

5.2.6 Scheduled Assessments H0649g

Baseline assessments included a complete medical history and physical exam, height, weight, Karnofsky performance status, vital signs , CXR, radiographic assessment of all sites of disease, hematology panel, chemistry panel.

Scheduled assessments of all sites of tumor were to be conducted at weeks 8, 16, 24, 36, 48 and every 12 weeks thereafter. The same method of assessment was to be used at each time point. Any patient with a CR or PR was to have their tumor assessment repeated 4 weeks later to confirm the response. CXR was to be performed at each time point.

Scheduled assessments of clinical status, medications, and adverse events were to be conducted weekly until study termination.

Scheduled hematology panel and chemistry panel testing was to be performed at weeks 1, 2, 4, 6, 8, and every 4 weeks thereafter until study termination. Scheduled laboratory tests were all performed by a central lab, [redacted] Any unscheduled testing was to be performed at the local laboratory. [Note: Only the data from testing done at [redacted] was submitted to the BLA; any unscheduled assessments were not included in the SAS data

sets; some of this data was hand written into the adverse event report or noted in particular patient narratives.]

Quality of Life questionnaires were administered at weeks 1, 12, 24, 36, 48, and every 12 weeks thereafter. These were self administered questionnaires consisting of the EORTC QLQ-C30 questionnaire (Version 1) and the EORTC Breast Cancer Module (BR-23).

Circulating shed antigen concentration was to be measured at baseline for all patients. Thereafter, only the first 50 patients who received the liquid formulation and the first 50 who received the lyophilized formulation had shed antigen tested at weeks 1, 2, 4, 8, and every 4 weeks thereafter.

Herceptin® serum concentration peak and trough levels were to be obtained in the first 50 patients who received the liquid formulation and the first 50 who received the lyophilized formulation weekly for the first 8 weeks then every 4 weeks thereafter.

Anti-Herceptin antibody testing was performed in all patients at baseline, weekly for the first 8 weeks then every 4 weeks thereafter.

5.2.7 Definitions of response H0649g

The protocol included definitions of complete response, partial response, minor response, stable disease and progressive disease. The FDA does not define minor response and includes such patients under the definition of stable disease. Please refer to Appendix D for definitions.

5.3 Results - Efficacy H0649g

There were 222 patients enrolled on H0649g with a goal of 200 patients. Of these 223 patients, 213 patients were treated with Herceptin®. Ten patients did not receive Herceptin® for the following reasons:

patient withdrew consent	2 patients
death	2 patients
clinically unstable	2 patients
increased bilirubin	1 patient
ineligible	3 patients (only 1 prior chemo; multiple myeloma; new brain metastases)

Of those patients who were treated with Herceptin®, 117 patients missed 253 doses; reasons for missed doses included:

hospitalization/illness	76 doses	(44 patients)

out of town/vacation	68 doses	(43 patients)
unable/unknown	21 doses	(14 patients)
allergic reaction	17 doses	(3 patients)
radiation treatment	12 doses	(3 patients)
patient refusal/cancel	8 doses	(5 patients)
death	2 doses	(2 patients)
drug not available	1 dose	(1 patient)
physician choice	1 dose	(1 patient)

5.3.1 Reasons for study discontinuation

Table 2 presents the reason for patient discontinuation from study H0649g.

Table 2. Reasons for discontinuation of therapy H0649g.

Reason for discontinuation	Number of patients
Death	15
Patient request	11
Adverse event	4
Abnormal labs	2
Lost to follow up	1
Other treatment	1

5.3.2 Demographics H0649g

Patient baseline characteristics are presented in Table 3. In order to facilitate comparison of the baseline characteristics of patients enrolled in the Phase 2 and 3 studies, the summary demographic data from H0648g is presented side by side with the demographic data from H0649g.

Table 3. Demographics H0649g

Parameter	H0649g H alone N=222	H0648g H + Chemo N = 235	H0648g Chemo alone N = 234
Karnofsky score at baseline			
100-80% (%)	88	83	80
70 and less %	11	14	18
HER2/neu expression			
+2 (%)	21	25	26
+3 (%)	75	75	74
Age			
median (yrs)	49	52	53
range (yrs)	28 - 81	25 - 77	25 - 75
Race N=222			
Caucasian %	82	89	90
African-American %	4	5	4
Asian %	4	2	1
Other %	7	4	5
Menopausal Status			
Pre %	54	39	42
Peri and Post %	41	61	56
Hormone Receptor Status			
ER or PR positive %	49	49	47
ER and PR negative %	36	34	34
Disease free period after diagnosis %			
< 1 year	36		
> 1 year	59		
> 5 years	7		
No. nodes at initial dx			
none %	18	26	28
1-3 %	40	23	21
4 or more %	21	36	38
Chemotherapy			
Adjuvant %	66	72	62
Metastatic Number of prior regimens for metastatic disease	1 = 32 2 = 67 3 = 0.5 4 = 0.5	0	0
Radiation therapy			
Adjuvant %	42	40	47
Metastatic %	39	24	25
Hormonal therapy			
Adjuvant %	28	40	38
Metastatic %	43	31	31
Transplant (BMT or PBSC) %	25	5	9

5.3.3 Efficacy Endpoints H0649

Overall response rate H0649g

The primary efficacy endpoint of H0649g is the overall response rate (patients achieving a CR or PR sustained for at least 4 weeks and confirmed by the REC). We reviewed the CRFs of all patients listed as responders. There were 2 patients who responded after the data cut off for the REC and we did not have the CRFs for these patients; we included them as responders even though we could not confirm this with the CRFs. Two patients were enrolled with chest wall disease which was very diffuse and difficult to measure; while these patients did not have measurable disease at baseline by our assessment we allowed them to be included in the analysis and they appear to have responded to the therapy due to the character of the improvement of their lesions. The FDA did not call one patient a responder because she received 4 separate courses of radiation treatment for bone pain and had new sites of disease on bone scan. Three responder patients noted as CRs by the REC were not called CRs by the FDA: two had pleural effusions on CXR and one had bone metastases at baseline without follow up studies to verify resolution of the bone metastases. There were 5 patients classified by the FDA as having complete responses and in all of these cases all sites of metastatic disease were located in soft tissue only (skin, lymph nodes). None of the patients with visceral or bone as sites of metastasis achieved a CR. There were 26 patients classified by the FDA as having partial responses. In some of these there were dramatic reductions in the size of hepatic metastases in particular.

Table 4. Primary Endpoint H0649g - FDA derived data set

Endpoint	Response rate	Ratio
Overall response by REC	14%	31/222
CR by REC	2%	5/222
PR by REC	12%	26/222

Survival and Time to Progression H0649g

The REC evaluation for time to progression is not present for many patients therefore the FDA is unable to perform a detailed review of the CRF's to confirm the time to progression data set. The same is true for time to treatment failure. Survival is presented in Table 5 and in Figure 1.

Table 5. Secondary Endpoints H0649g - Sponsor derived data set

Endpoint	Median (months)	CI (months)
Time to Progression	3.1	2.3 - 3.4
Time to Treatment Failure	2.3	1.9 - 3.0
Survival	12.8	9.9 - ongoing

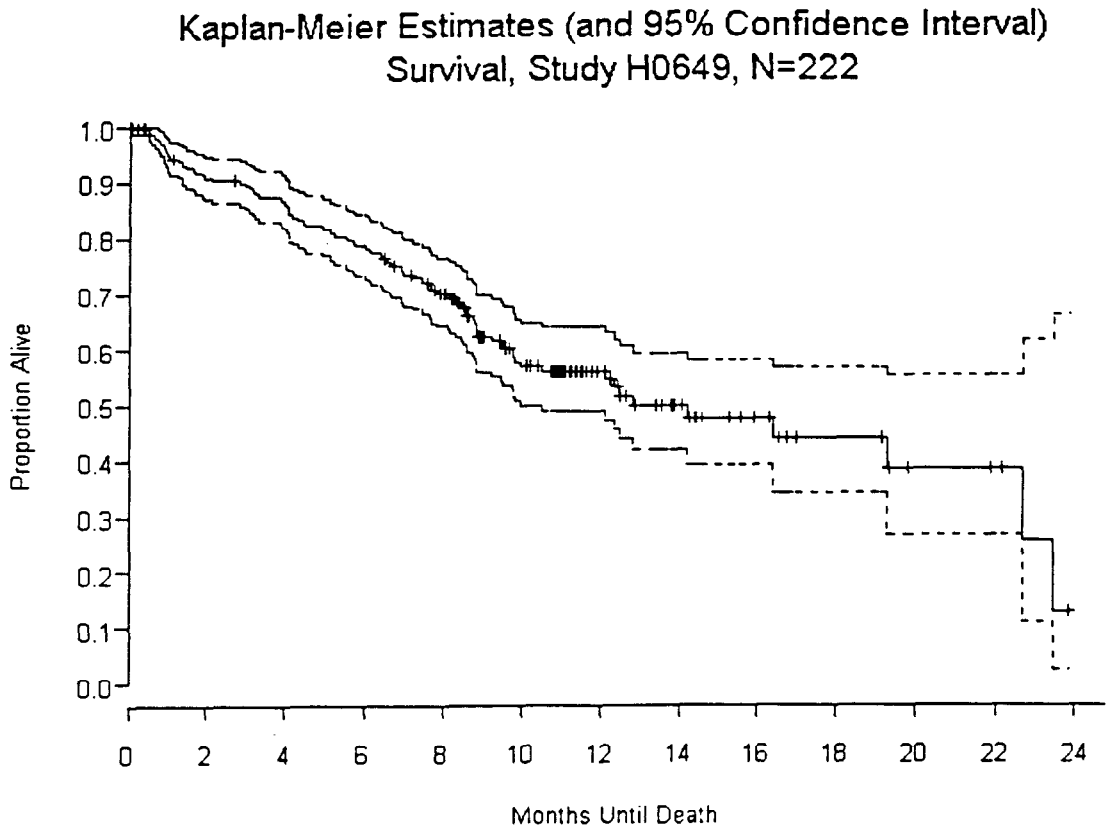

Figure 1. Kaplan-Meier estimate of survival for patients enrolled on study H0649g. The dashed lines represent the upper and lower 95% confidence intervals and the solid line is the survival plot.

Immunohistochemistry testing for protein overexpression of HER2/neu

As a selection criterion for patients enrolled on H0649g, the presence of HER2/neu protein over-expression in tumor biopsies based upon IHC reading scores of 2+ or 3+ (on a 0 - 3+ scale) was required. The majority of patients, 172, were scored as 3+ and of these there were 29 responders (17%); 50 patients were scored as 2+ and of these there were 2 responders (4%). See Section 7.0 for details of HER2 protein detection and an integrated summary of efficacy results for patients with 2+ relative to 3+ overexpressing tumors.

5.4 Results - Safety H0649g

5.4.1 Adverse events - overall

Adverse events were assessed from the SAS data sets provided by the sponsor. The events presented in Table 6 were those reported by the investigators in the adverse event reporting forms of the CRF's. Patients who developed PD could continue on Herceptin® treatment with or without chemotherapy or hormonal therapy; consequently the adverse events are reported for all patients while on study and for all patients until the time of PD only.

Table 6. Adverse events H0649g.

Gastrointestinal Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Diarrhea	33	25 (8)
Abdominal pain	28	24 (9)
Dyspepsia	14	11 (3)
Jaundice	4	2 (1)
Abdomen enlarged	3	2 (1)
GI disorder	3	1 (1)
Hepatic failure	3	2 (2)
Liver tenderness	3	3 (0.4)
Gastroenteritis	2	1 (0.4)
Rectal disorder	2	2 (0)
Rectal hemorrhage	2	1 (0)

Hematologic Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Anemia	11	5 (4)
Leukopenia	8	3 (3)
Thrombocytopenia	2	0 (0)

Cardiac Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Increased cough	36	30 (11)
Dyspnea	30	22 (15)
Chest pain	28	22 (11)
Peripheral edema	16	11 (3)
Tachycardia	9	6 (1)
Edema	9	5 (2)
Pleural effusion	9	7 (7)
Hypotension	5	3 (1)
Palpitations	4	2 (1)
Hypertension	4	2 (1)
Congestive heart failure	3	2 (2)
Cardiomyopathy	2	1 (1)
Cardiovascular disorder	2	1 (0.4)
Heart arrest	2	0.4 (0.4)

Allergy Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Rash	19	15 (7)
Rhinitis	18	15 (3)
Pruritus	14	12 (2)
Allergic/Anaphylactoid reaction	5	2 (1)
Edema of the face	3	2 (0.4)
Urticaria	3	2 (0.4)

Constitutional Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Any "pain"	81	77 (53)
Pain	58	51 (31)
Asthenia	56	49 (25)
Fever	47	40 (13)
Nausea	46	36 (13)
Chills	38	36 (15)
Vomiting	32	26 (8)
Headache	31	25 (9)
Anorexia	21	14 (5)
Insomnia	20	16 (6)
Depression	12	9 (5)
Nausea and vomiting	10	8 (3)
Alopecia	6	5 (2)
Dehydration	5	3 (1)
Sweating	5	4 (0.4)
Weight loss	5	3 (2)
Malaise	4	3 (0.4)
Chills and fever	3	3 (2)
Weight gain	2	1 (0.4)

Infection related Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Infection	25	19 (8)
Pharyngitis	19	14 (4)
Urinary tract infection	7	3 (1)
Bronchitis	6	3 (2)
Pneumonia	5	2 (1)
Herpes simplex	3	2 (0.4)
Cellulitis	2	1 (0.4)
Gastroenteritis	2	1 (0.4)
Herpes zoster	2	2 (2)
Sepsis	2	1 (0.4)

Mucositis Adverse event term	Percent of all patients with the adverse event (all grades)	Percent of patients treated to time of first progression (percent of same with mod/sev event)
Any stomatitis	11	6 (1)
Taste perversion	5	2 (0.4)
Dry mouth	4	3 (1)
Mucous membrane disorder	4	0.4 (0)
Esophagitis	3	1 (0.4)
Dysphagia	3	2 (1)
Oral moniliasis	3	2 (1)
Moniliasis	2	1 (1)
Mouth ulceration	2	2 (0.4)

5.4.2 Cardiotoxicity

Cardiotoxicity was seen in patients treated with Herceptin® as a single agent. The incidence was found to be 14 out of 213 treated patients or 6.6%. Prior anthracycline therapy was administered to 12 patients, prior chest radiation therapy to 10 patients and prior history of cardiac or cardiac related risk factors was present in 7 patients. The median cumulative doxorubicin dose was 368 mg/m^2 (95% CI 138, 560). By comparison, the median cumulative doxorubicin dose for patients who did not experience a cardiac event was 282 mg/m^2 (95% CI 79, 525). The collection of data for prior chest radiation therapy and cardiac related past medical history was not as aggressively obtained as it was for the patients who experienced cardiotoxicity; therefore, it is difficult to make comparisons of these parameters. The two patients who had not received prior anthracycline therapy had positive past medical histories (one had pre-existing CHF with an EF of 37% and one had suspected CAD) and had received prior radiation therapy. Employing the NYHA system, classification of the most severe cardiac event experienced by patients reveals the following:

Class I	1 patient
Class II	3 patients
Class III	1 patient
Class IV	9 patients

Therapy for cardiac disease was administered in 11 patients and 2 patients required treatment with dopamine and dobutamine. Two deaths were attributed to cardiac disease. One patient underwent endomyocardial biopsy which on electron microscopy revealed myocyte vacuoles and z-bands.

6.0 CLINICAL TRIAL H0648g - PHASE 3, TWO ARM STUDY AND THE COMPANION EXTENSION STUDY H0659g

6.1 Title H0648g

Chemotherapy and Antibody Response Evaluation (CARE): A Phase III, Multinational, Randomized Study of Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) Combined with Chemotherapy in Patients with HER2 Overexpression who have not Received Cytotoxic Chemotherapy for Metastatic Breast Cancer.

Enrollment conducted from June 12, 1995 to March 7, 1997; patient follow up is still ongoing.

6.2 Title H0659g

An additional study serves as and extension trial to H0648 and it is **H0659g**: An Open Label Extension Study with Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) For Patients Whose Metastatic Breast Cancer Progressed During Treatment on Study H0648g.

Enrollment conducted from December 1995 and is still ongoing.

6.3 Study design and conduct of H0648g

6.3.1 Objectives

Primary endpoint

Time to disease progression was defined as the time from randomization until documented disease progression or death. For patients who discontinued the study prior to PD and had no assessment performed after baseline, time to progression was censored at the time of last treatment date or date of study termination. All other patients were censored at the time of last assessment.

Secondary endpoints

Overall response rate was defined as CR + PR sustained for 4 weeks.

Duration of major response was defined as time from initial CR or PR until PD or death, whichever occurred first.

Time to treatment failure was defined as the time from randomization to whichever of the following occurred first:

- Documented PD
- Treatment discontinuation due to adverse event
- Patient's request to discontinue study
- Patient death
- Commencement of concurrent immunotherapy, chemotherapy, or hormonal therapy not specified in the protocol.

Survival was defined at the time from randomization to death.

Quality of Life as determined by a questionnaire which included the following:

EORTC QLQ-C30 Core Questionnaire, version 1
EORTC breast cancer module BR-23
Selected items from the Breast Cancer Questionnaire BCQ
Selected items from the National Health Institute Survey
Several original items

6.3.2 Design H0648g

This was a Phase 3, open label, randomized study comparing therapy with Herceptin® plus chemotherapy with chemotherapy alone and employing two different chemotherapy regimens depending on the patient history of anthracycline use. The study was conducted at 150 sites in North America, Europe, and Australia/New Zealand. The target enrollment was 450 patients.

6.3.3 Major amendments made to the study H0648g and selection criteria

H0648g began as a randomized double blind study with clearly outlined entry criteria; the two arms of the trial were anthracycline/cyclophosphamide (AC) chemotherapy combined with herceptin and AC with placebo. However, multiple major changes in the protocol were enacted during the conduct of the study, the majority of which were added after 97 patients had enrolled. In its final form it was an open label study with relatively broad entry criteria employing two different chemotherapy regimens. While there were still two arms to the study (in terms of randomization), there were 4 clinically distinct subgroups: AC + Herceptin®, AC alone, paclitaxel (T) + Herceptin®, and paclitaxel (T) alone. In addition, study H0659g was initiated in order to enable all patients from H0648g meeting eligibility criteria for H0659g to receive Herceptin®. Below is a table comparing the original and final study designs for H0648g.

Table 7. Comparison of original protocol and final protocol H0648g.

Parameter	H0648g original study Initiated May 1995	H0648g final study May 1996
Randomized	Herceptin vs placebo	Herceptin vs control
Blinding	Double Blind	Open label with blinded REC
Placebo	Yes	No
Chemotherapy	AC	AC or T if prior anthracycline
Number of cycles of chemo	6	at least 6 with no limit
Target enrollment	450	450
Primary endpoint	Time to progression	Time to progression
Secondary endpoints	Overall response Duration of response Survival at one year	Overall response Duration of response Survival at one year
KPS	60 or better	60 or better
HER2 expression	2+ or 3+; Ab 4D5	2+ or 3+, Ab 4D5 or CB11
Prior anthracycline (adjuvant)	No	Yes
Prior chemo for metastatic disease	No	No
Prior hormonal therapy for metastatic disease	> 2 weeks prior	No limit
Prior radiation therapy for metastatic disease	> 2 weeks prior	No limit
Bi-dimensionally measurable disease	Yes	Yes
Bone metastases as sole site of disease	No	Yes, lytic lesions only
Brain metastases	No	Yes if treated and stable
Baseline labs and clinical studies	Creatinine < 1.7 Bilirubin < 2.0 Protime < 14 WBC > 3500 Platelets > 100,000 Hgb > 10 Calcium > 11.0 FEV_1 > 60% of predicted Cardiac EF > 45%	"Suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening lab assessments of hematologic, renal, hepatic, and metabolic functions."
NYHA Class III or IV CHF	No	No limit
Herceptin administration relative to chemo	Herceptin given one day prior to chemo for all cycles	Herceptin give day prior for first cycle then at the same time as chemo for subsequent cycles
Tumor assessment times	Weeks 8, 17, 26, 36, 52, then every 12 weeks	Weeks 8, 20, 32, 44, 56, then every 12 weeks
Extension study H0659g	No	Yes, initiated November 1995

According to the sponsor, enrollment on the trial was very slow and they had determined that the reasons related to investigator and patient concerns. The sponsor decided that the above outlined amendments were necessary in order to improve the rate of enrollment. However, this resulted in a study which was difficult to analyze for a variety of reasons. Below are listings of the reasons proposed by the sponsor for making the extensive modifications of the ongoing clinical trial and problems which this created for the analysis of the study.

Reasons for making the changes:

1. The rate of enrollment was very slow.
2. Only 25-30% of patients screened will be HER2/neu positive making enrollment even more difficult.
3. Many patients have received adjuvant anthracycline therapy
4. Patients and investigators object to the placebo; it is difficult to justify the weekly infusion of a placebo in terms of quality of life issues.
5. Patients and investigators want patients to all have the opportunity to receive Herceptin®.

Factors complicating the analysis of the data

1. While the addition of the REC helped obviate some of the problems of an open label study, the REC did not evaluate a given patient until the investigator determined that progressive disease was present and referred the patient to the REC. Thus, since not all patients had progressed at the time of BLA filing (approximately 69 patients), there were missing REC evaluations for ~14% of enrolled patients of which nearly 2/3 were in the Herceptin® arm. The FDA requested that the sponsor have the REC read films of all unread cases and re-read films from a randomly selected set of already read cases in order to minimize bias. These data were submitted to the FDA and included in the FDA review.
2. The patients treated with paclitaxel were by definition in a different prognostic group as they had all received adjuvant anthracyclines. Thus, the baseline characteristics differed markedly between paclitaxel and AC patients regardless of assignment to Herceptin® therapy or not.
3. The evaluation relied heavily upon subgroup analyses due to differences in baseline characteristics and safety profiles as well as possible inherent differences in activity of the two different chemotherapy regimens when combined with Herceptin®.
4. Broadening of the eligibility criteria placed the study at risk for enrollment of patients with decreased estimated survival and, therefore, may have obscured the potential benefits; if a disproportionate number of such patients were entered into one arm over the other resulting in an imbalance, the results may have been swayed by the imbalance.
5. Elimination of baseline studies for cardiac and pulmonary function prevented a more informative safety analysis.
6. Changes in the timing of tumor assessments could change the time to progression endpoint in favor of a longer time to progression.
7. Interpretation of the survival analysis was limited at the time of progression on H0648g due to cross over of control arm patients to Herceptin® on H0659g.
8. Patients on the Herceptin® arm were seen weekly at a minimum whereas those on the control arm were seen every 21 days at a minimum; the increased frequency of contact in the treatment arm could have affected the reporting rate of adverse events. There may have been more events reported from patients on the Herceptin® arm, in part, due to the more frequent contact with health care professionals and this would have created bias in favor of the control arm.

6.3.4 Treatment H0648g

Herceptin® was administered as an intravenous infusion in the outpatient setting. The initial loading dose was 4 mg/kg infused over 90 minutes with a one hour observation period. If the first dose was well tolerated all subsequent infusions were administered weekly at a dose of 2 mg/kg infused over 30 minutes with a 30 minute observation period for the second dose and no observation thereafter. If the initial or maintenance infusions were not well tolerated then all subsequent infusions were infused over 90 minutes. Doses were to be adjusted for changes in the patient weight, but no dose reductions were designated for adverse events; a dose was either administered or held.

Chemotherapy was administered on the day following the first Herceptin® infusion. Patients were treated with either AC (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus cyclophosphamide 600 mg/m^2) or if they had received prior anthracycline therapy they received T (paclitaxel 175 mg/m^2 over 3 hours). For all subsequent cycles, Herceptin® was administered immediately prior to chemotherapy rather than the day prior and the length of the infusion was decreased to 30 minutes assuming the initial 90 minute infusion was tolerated well. Chronic low dose steroid use and prophylactic dexamethasone were permitted. Chemotherapy was administered every 21 days for a minimum of six cycles and a maximum number to be determined by the investigator at the site. The investigator was expected to proceed in a manner consistent with standard of care.

6.3.5 Concomitant therapy

Radiation therapy to localized sites of disease could be administered to patients if medically necessary during the study provided the sites radiated were not used by the investigator to evaluate tumor response or were not sites of new pathologic fracture in which case the patient would have progressive disease.

Non-protocol defined chemotherapy, hormonal therapy, immunotherapy or radiation therapy was not allowed; patients were to be classified as treatment failures at the time of institution of such therapy.

6.3.6 Method of assessment

Tumor response was evaluated by the investigator at weeks 8, 20, 32, 44, then every 12 weeks thereafter. Studies were to be repeated four weeks after an initial response was noted in order to confirm the response. The same method of evaluation was to be used at all time points. The investigator assessment was recorded on the CRF as CR, PR, MR, SD, or PD; no tumor measurements from the investigator were included. Once a patient developed PD, their studies and clinical data were sent to the REC for determination of response and progression. Patients were required to have REC confirmed progression prior to entering the extension study H0659g.

6.4 Study H0659g

Once a patient on H0648g progressed as determined by the REC, she could choose to enroll in H0659g, the extension study. On H0659g she has two options for therapy: 1) Herceptin® 2mg/kg weekly and 2) Herceptin 2mg/kg weekly combined with an anti-tumor regimen of the investigator's choice. Entry criteria were as follows: AGC > 1500, plt > 100,000, bili < 1.2. Primary endpoint was safety. Secondary endpoints were overall response rate (OR), duration of response, TTP, TTF, survival , survival at one year.

Chemotherapy agents used included the following:

Agent	Number of Patients
Carboplatin	5
Cisplatin	14
Cyclophosphamide	11
Docetaxel	18
Doxorubicin	14
Epirubicin	2
Etoposide	1
Fluorouracil	14
Gemcitabine	4
Leucovorin	2
Methotrexate	8
Mitomycin	4
Mitoxantrone	1
Paclitaxel	35
Thiotepa	1
Vinblastine	2
Vinorelbine	27

6.5 Methodology of Data Review H0648g

During the review process the following deficiencies were noted which led to the decision to conduct an intensive review of the primary data (CRFs):

a) Of 20 randomly selected patients with cardiac dysfunction, 70% had missing values for ejection fractions; this was felt to reflect the deficiencies in the ejection fraction data set as a whole and was deemed inadequate for review. Genentech has since submitted a more complete data set.
b) There was no specific adverse event term for neutropenic fever or neutropenic sepsis.
c) Patients who required growth factors (G-CSF or GM-CSF or erythropoietin) were not necessarily listed as having anemia or neutropenia on the adverse event forms and vice versa.
d) Patients who required transfusions were not necessarily listed as having anemia or thrombocytopenia on the adverse event forms and vice versa.
e) The reasons for discontinuation of therapy were often in text form.
f) The REC determination of responses was limited by the studies which they were provided.
g) The investigators did not always image all sites of disease at every time point.
h) Clinical exam or symptoms relevant to progression as well as concomitant therapy information were not necessarily given to the REC and may bear on determination of progression.
i) Elements of the REC charter resulted in inaccurate assessments of response in some patients. Criteria used to determine response were not always consistent with standard practice. For example, a patient with pleural effusion as a site of disease who had a complete response of her liver lesions was called a CR by the REC despite the ongoing presence of the pleural effusion; the REC charter requires that there be pathologic proof that the effusion is malignant. If there is no other evidence for a cardiac etiology for the effusion, the FDA views this patient as a PR and not a CR.
j) Determination of sites of disease was made by the sponsor with the assumption that distal lymph nodes would be classified as visceral disease whereas standard practice would call this soft tissue disease or, using the protocol terminology, superficial disease.

6.6 Results H0648g

6.6.1 Enrollment:

469 pts enrolled at 119 sites between June 12, 1995 and March 7, 1997

[Problems with the enrollment data included the inability to match up sites with investigators with patients (now resolved), and multiple patients assigned the suffix number 3001 or 3002 (now resolved).]

464 pts treated

2 pts withdrew consent (1 Herceptin, 1 control)
1 pt enrolled in wrong study; intended for study H0649g (1 control)

1 pt diagnosed with colon cancer (1 control)
1 pt died (1 Herceptin)

2 arms: Chemotherapy plus Herceptin®
Chemotherapy alone

4 subgroups

AC plus Herceptin	143	
AC alone	138	
Paclitaxel plus Herceptin	92	(1 pt anaphyl.to 1st T dose then got AC)
Paclitaxel alone	96	

7 sites had 10 or more patients

H0659g

157 patients (33%) went on to be enrolled in H0659g, the extension study, as of the date of the BLA filing. More patients who had been on the control arm of H0648g enrolled in H0659g compared to those who had been on the treatment arm of H0648g. The H0659g enrollment numbers listed by previous therapy on H0648g are as follows:

Original Treatment Arm	Number of Patients Enrolled in H0659g
AC-Herceptin®:	23
AC alone:	51
T-Herceptin®:	22
T alone:	61
Chemo-Herceptin®:	45
Chemo alone:	112

6.6.2 Demographics H0648g

Table 8 presents the baseline characteristics of all patients enrolled on H0648g.

Table 8. Demographics - H0648g

Parameter	AC + H N = 143	AC N = 138	T + H N = 92	T N = 96	*Chemo+H N = 235*	*Chemo N = 234*
Karnofsky score at baseline						
100-80% (%)	81	78	86	84	*83*	*80*
70 and less %	15	20	12	14	*14*	*18*
HER2/neu expression						
+2 (%)	24	30	26	20	*25*	*26*
+3 (%)	76	70	74	80	*75*	*74*
Age						
median (yrs)	53	54	50	50	*52*	*53*
range (yrs)	27 - 76	25 - 75	25 - 77	26 - 73	*25 - 77*	*25 - 75*
Race						
Caucasian %	89	90	90	90	*89*	*90*
African American %	7	4	2	3	*5*	*4*
Asian %	<1	1	3	1	*2*	*1*
Other %	4	4	4	6	*4*	*5*
Menopausal Status						
Pre %	31	40	52	46	*39*	*42*
Peri and Post %	69	59	48	53	*61*	*56*
Geographic Region						
N. Am. %	63	61	80	86	*70*	*71*
Europe %	28	30	13	7	*22*	*23*
Aust/ New Z.%	9	9	7	6	*8*	*8*
Hormone Receptor Status						
ER or PR + %	50	49	49	45	*49*	*47*
ER and PR -	31	28	40	42	*34*	*34*
Years from primary dx to metastatic disease						
Median	2.3	2.2	2.0	1.7	*2.1*	*2.0*
Range	0 - 18.5	0 - 18.7	0 - 16.4	0.4 - 8.5	*0 - 18.6*	*0 - 18.7*
No. nodes at initial dx						
none %	35	40	13	10	*26*	*28*
1-3 %	22	18	25	24	*23*	*21*
4 or more %	24	22	54	60	*36*	*38*
Prior Surgery						
Lump. %	22	29	12	11	*18*	*22*
Mast. %	67	57	85	87	*74*	*69*
None	11	13	2	1	*8*	*8*
Adjuvant Chemo %	57	36	96	99	*72*	*62*
Adjuvant XRT %	32	36	53	64	*40*	*47*
Adjuvant Horm. %	39	33	43	45	*40*	*38*
Transplant (BMT or PBSC) %	0	0	13	22	*5*	*9*
Metastatic Horm. %	34	34	26	27	*31*	*31*
Metastatic XRT %	23	24	25	26	*24*	*25*

6.6.3 Sites of metastatic disease H0648g

The sponsor classified the sites of metastasis for each patient prior to randomization for purposes of stratification. The sites defined were visceral, superficial and bone only. The sponsor defined these sites as follows:

Visceral disease:	organ involvement (liver, lung, omentum, etc), distal lymph nodes (cervical, supraclavicular, axillary, mediastinal), breast tumors
Superficial disease:	skin, chest wall
Bone only disease:	lytic, bi-dimensionally measurable bone disease with no other sites of disease

Since these definitions differ somewhat from standard practice, the FDA analyzed the data using the following definitions in order to ensure a non-biased distribution between the 2 arms of the study:

Visceral disease:	organ involvement (liver, lung, omentum, etc.), mediastinal lymph nodes
Soft tissue disease:	distal lymph nodes (cervical, supraclavicular, axillary), skin, chest wall, breast
Bone only disease:	lytic, bi-dimensionally measurable bone disease with no other sites of disease
Bone disease:	involvement of any bone with tumor

In addition, the FDA evaluated additional subgroups for sites of disease to assess for a balance of prognostic factors. This analysis demonstrates that the balance was maintained between the subgroups (ACH vs. AC, TH vs. T) and the two randomization arms (H + Chemo vs. Chemo). The only slight imbalance was for patients who have all three sites of disease present at the time of entry in which case the bias falls with more of these patients enrolled on the Herceptin® arms.

Table 9. Sites of metastatic disease H0648g - FDA analysis

Site of disease	ACH N = 143 n, (%)	AC N = 138	TH N = 92	T N = 96	Chemo + Herceptin N = 235	Chemo alone N = 234
Visceral ± other	115 (80)	107 (78)	68 (74)	74 (77)	183 (78)	181 (77)
Soft tissue ± bone	18 (13)	22 (16)	17 (18)	15 (16)	35 (15)	37 (16)
Bone only	10 (7)	8 (6)	6 (7)	6 (6)	16 (7)	14 (6)
Other subgroups						
Visceral and soft tissue and bone	22 (15)	17 (12)	9 (10)	7 (7)	31 (13)	24 (10)
Soft tissue alone	12 (8)	15 (11)	11 (12)	11 (11)	23 (10)	26 (11)
Visceral alone	65 (45)	54 (39)	34 (37)	34 (35)	99 (42)	88 (38)

6.6.4 Protocol Violations, early deaths, and other issues

The following is a list of those patients for whom there was less than 30 days follow up, no treatment administered or who died before documented progression (N=22). Early death was defined as death within the first 30 days. A total of 11 patients experienced early death and of these 7 were in the Herceptin® arm and 4 were in the control arm.

Protocol Violations/noncompliance:	13 patients (9 herceptin, 4 control)
Withdrew consent:	3 patients (2 herceptin, 1 control)
Lost to follow up:	3 patients (3 herceptin)
Randomized to wrong study:	1 patient (1 control)
Other:	2 patients (2 herceptin)

Sixteen of these patients fall in the Herceptin plus chemo arm and 6 in the chemo alone arm. In the final data analysis, the result would tend to favor the control arm. A short summary of relevant factors for each of these patients is outlined below.

[* indicates the 16 patients that the sponsor did not include in their evaluable population]

[redacted] : AC + Herceptin
Died 6 months after enrollment; cause of death not described well.
Patient refused therapy after 4 months. Best response was PR.

* [redacted] Taxol + Herceptin
Died one week after first treatment and enrollment
Baseline SGOT = 676 (gd 4) and SGPT = 455 (gd 4)
Allergic reaction to Herceptin at first dose
Chest pain, hemoptysis, SOB indicative of possible PE

* [redacted] Taxol alone
Died 4 days after first treatment (18 days after enrollment)
Baseline physical : abd protuberant, liver 11 cm below RCM, verbally slow. H/o alcoholism. Hypercalcemic. No labs.

* [redacted] AC + Herceptin
Died 7 days after first treatment (14 days after enrollment)
Pt had altered mental status for a few weeks prior to entry and was lethargic with slurred speech on first day of therapy, but still treated. Admitted 3 days after chemo with neutropenia, thrombocytopenia (plt= 4) and gram negative sepsis; MRI brain showed meningeal carcinomatosis; she developed ARDS and died.

* [redacted] Control
Discontinued 3 days after enrollment due to diagnosis of concurrent colon cancer.

* [redacted] AC
Died 3 days after treatment (19 days after enrollment)

No labs but investigator noted that patient's bilirubin and LFT's were too high to receive AC and he/she decided to treat the patient with CMF instead.

* Taxol + Herceptin
Died 7 days after first treatment and enrollment.
On day of Taxol therapy c/o malaise, lethargy and diarrhea.
Admitted 4 days after chemo with pancytopenia and sepsis; experienced multiple cardiac arrests and died. No labs.

AC + Herceptin
Died 10 months after enrollment; cause of death not described well. Best response was SD with no determination of PD by REC.

AC + Herceptin
Date of death not known.
INV determined PD after 4 months but REC never determined PD.
Pt still entered onto H0659g.

AC + Herceptin
Died 15 months after enrollment. Patient treated in England but was from Spain. Best response was PR. Patient refused further therapy after 6 months and returned to Spain.

* Control
Randomized to the wrong clinical study. Intended for H0649g.

* AC + Herceptin
Died 12 days after first treatment (16 days after enrollment)
Baseline SGOT = 390(gd 4) bilirubin = 6.4 (gd 3) and
alk phos = 912 (gd 3). Full dose of Epirubicin administered.
Admitted with neutropenic sepsis 9 days after chemo and died the following day.

* Taxol + Herceptin
Died 3 or 4 months after enrollment.
At baseline patient had no measurable disease and clear evidence of liver failure with ascites and a prolonged PTT. She was enrolled as a protocol exception. REC unable to determine response to therapy.

* AC + Herceptin
At baseline the patient was diabetic and on chronic low dose prednisone for thrombocytopenia. She received 2 doses Herceptin

and one dose Taxol following which she was hospitalized for dehydration, nausea and vomiting which developed into hyperosmolar coma with a Na = 170, K=5.2, Glucose >650, Creatinine = 5.9 (previously these labs had been normal); concurrently she was neutropenic and thrombocytopenic. She was then noted to have an infection of her breast implant. There is no further information on this patient and she was lost to follow up.

* Taxol + Herceptin
Died 8 days after first treatment (9 days after enrollment)
Admitted with liver failure prior to study entry; enrolled while in the hospital with baseline labs alk phos = 528 (gd 3), SGOT = 1026 (gd 4). Overdosed with paclitaxel; she was given 170% of the intended dose.

* Herceptin
Patient withdrew consent.

AC + Herceptin
Died 10 months after enrollment. Cause of death unclear whether due to cardiac failure or progressive disease and liver failure. Pt developed severe cardiomyopathy with fall in EF from 50% to 11%. Best response was SD. Patient refused follow up CT scans at week 12.

AC + Herceptin
Died 13 days after first treatment (18 days after enrollment)
At baseline patient required drainage of ascites. Enrolled with notation of protocol exception for elevated bilirubin (37 nmol); SGOT = 338 (gd 3). Treated with reduced dose of doxorubicin at 47% of intended dose. Admitted for neutropenia and fever 10 days after chemo. Cardiac arrest 5 min after receiving Ceftazidime. Autopsy: congestive heart failure (no ischemic disease) secondary to renal failure secondary to neutropenia and sepsis.

AC alone
Died 27 days after first treatment (29 days after enrollment)
At baseline patient had ascites. Received 32% of intended dose of doxorubicin on days 0, 14, and 21 (instead of every 21 days). Admitted for neutropenia and sepsis 4 days after last chemo and died 2 days later.

* Herceptin
Died 21 days after enrollment. Deteriorated rapidly after enrollment and was never treated with Herceptin or chemo.

Developed lymphangitic spread of tumor in the pulmonary tree and died with respiratory failure.

* [redacted] Control
Patient withdrew consent.

* [redacted] Taxol alone
Died 14 days after first treatment (28 days after enrollment)
On study day -7 creatinine = 0.7 but on day 0 Cr = 4.4. Patient was treated anyway. The next day admitted with acute renal failure and subsequently developed pancytopenia, liver failure, cardio-pulmonary failure and died and the 13th hospital day.

Other patients deemed not evaluable by sponsor:

* [redacted] Taxol
Patient's tumor assessment was by physical exam only. The investigator conducted exams at week 0 and again at the patient's urging at week 1 with one of the chest wall lesions increasing in size from 1x1 to 1.5x1 which qualifies as PD; there was no photographic evidence of progression. Patient had no further evaluation and was entered onto H0659g.

* [redacted] Taxol + Herceptin
The patient received one dose of Herceptin and one dose of Taxol and experienced multiple severe adverse events including dehydration, severe mucositis, neutropenia and sepsis. She withdrew her consent.

As can be noted from the vignettes above, 13 of these patients were inappropriately enrolled into this trial by the standards of oncology practice and were quite ill at the time of enrollment. Consequently, the early deaths were expected based upon the baseline clinical status of the patients and were not due to Herceptin® administration. It is the opinion of the reviewer that the major amendment to the protocol in which many selection criteria were eliminated played a significant role in creating this problem. Of these 13 patients, 9 were in the Herceptin® arm and 4 were in the control arm.

6.6.5 Concomitant therapies

The protocol clearly states that no other anti-tumor therapy was permitted until the patient was deemed to have progressive disease by the REC; administration of such therapy to a patient rendered them a treatment failure. Table 10 below summarizes events of concomitant therapy administered to patients prior to the diagnosis of progressive disease and their distribution relative to the treatment arms, Herceptin® plus chemo vs chemo alone. In particular, there was a bias with 19 vs 7 patients on the chemo alone arm vs the Herceptin® plus chemo arm, respectively. Types of chemotherapy administered included

the following: vinorelbine, docetaxel, CMF, mitoxantrone/5FU/LCV, weekly doxorubicin, paclitaxel, and cyclophosphamide.

Table 10. Concomitant therapy by study arm H0648g.

Type of concomitant therapy	Herceptin plus chemo	Chemo alone
Cytotoxic chemotherapy	1	8
Tamoxifen	3	3
Megestrol acetate	2	5
Anastrozole	1	2
Goserelin acetate	0	1
Total	**7**	**19**

6.6.6 Dose Intensity

While the majority of patients received 6 cycles of chemotherapy, there were a number of patients who received more or less than 6 cycles particularly after the major amendment to the protocol allowing for additional cycles of therapy beyond six. The summary data for cumulative dose and number of cycles of therapy is presented in Table 11. Due to the difference in dosing for doxorubicin and epirubicin these data are presented in separate columns.

Table 11. Cumulative dose for anthracyclines and paclitaxel H0648g

Parameter	ACH - dox mg/m2	AC - dox mg/m2	ACH - epi mg/m2	AC - epi mg/m2	TH mg/m2	T mg/m2
Mean cumulative dose	319 ± 111	314 ± 99	438 ± 131	428 ± 172	1077 ± 580	855 ± 510
Median cumulative dose	49	352	446	447	1036	864
Range of cumulative doses	29 - 688	58 - 525	76 - 760	143 - 757	172 - 3415	7 - 2875
Median number of cycles	6	6	6	6	6	5
Range of number of cycles	1 - 12	1 - 10	1 - 10	2 - 10	1 - 20	1 - 17
Number of patients with > 6 cycles	20	18	3	5	28	20

6.6.7 Reasons for Therapy Discontinuation H0648g

In analyzing the reason why patients may have discontinued their chemotherapy and/or Herceptin® therapy, two approaches were taken. The first approach was a two part examination of the data: a) evaluate all those patients who completed their course of chemotherapy and continued on Herceptin® and b) evaluate all those patients who did not complete the minimum 6 cycles of chemotherapy and note the reasons for stopping chemo, Herceptin® or chemo and Herceptin®. These data are presented in Tables 12 and 13. The second approach was to view each arm of the study as a single therapy i.e. "AC plus Herceptin®" or "AC plus best supportive care"; then evaluate all patients who stopped either chemo or herceptin for reasons other than progressive disease, specifically death, adverse event, or patient request. These data are presented in Table 14. For patients who stopped their therapy prior to completing the minimum six cycles of chemo for reasons other than progressive disease, there was fair balance between all subgroups for adverse event and patient request; for death, 6 in the ACH arm and 2 in the AC arm stopped. For patients who completed chemotherapy and were on maintenance Herceptin®, 14 patients stopped Herceptin® in the ACH arm for adverse event and notably none did so in the TH arm; a similar result is seen in Table 14 where the adverse event data were the driving difference between the ACH and AC arms. There was fair balance for reasons of death and patient request.

Table 12. Patients who stopped therapy prior to completing 6 cycles of chemo H0648g

Reason to stop	ACH N = 143	AC N = 138	TH N = 92	T N = 96
Adverse event chemo +/- H stopped	4	2	3	1
Patient request chemo +/- H stopped	5	3	2	3
Death	6	2	3	3
Adverse event chemo stopped	5	n/a	4	n/a
Patient request Herceptin stopped	0	n/a	1	n/a

Table 13. Patients who completed chemotherapy and then stopped Herceptin H0648g

Reason to stop	ACH	AC	TH	T
Adverse event	14	n/a	0	n/a
Patient request	7	n/a	5	n/a
Death	2	n/a	1	n/a

Table 14. Reasons for stopping therapy, chemo or Herceptin® or both H0648g

Reason to stop	ACH n, (%)	AC	TH	T	H + Chemo	Chemo alone
Adverse event	24 (17) [7 chemo only]	2 (1)	6 (7) [4 chemo only]	2 (2)	30 (13)	4 (2)
Patient request	12 (8)	6 (4)	5 (5)	3 (3)	17 (7)	9 (4)
Death	8 (6)	11 (8)	4 (4)	5 (5)	12 (5)	16 (7)

6.6.8 Primary Efficacy Endpoint H0648g

The primary endpoint of H0648g was the time to disease progression. We conducted two different analyses of this endpoint. The first analysis (Table 15) employed the sponsor derived SAS data sets with a data cutoff point of December 1997 (some of the data proceeds into 1998). The second analysis (Table 16) employed an FDA data set derived from the analysis of the case report forms which have a data cut off of December 31, 1997. The FDA reviewed each case report form using the REC measurements and comments, known sites of disease, patient symptoms, hospitalizations, and deaths to determine the time to progression for each patient; in addition, imaging studies were reviewed in approximately 4 % of cases. Kaplan-Meier curves for time to progression appear in Figures 2, 3, and 4.

In situations in which there were no specific tumor measurements that could be relied upon and judgement was required to make an assessment of time to progression, the FDA defined the following scenarios as NOT fulfilling the definition of progressive disease:

a) a new pleural effusion or ascites which subsequently disappeared on later imaging studies in the absence of a thoracentesis or pericentesis.
b) pleural effusions which were transudative or possibly due to another etiology such as congestive heart failure or infection
c) bone lesions followed with plain films only, provided the plain films were performed at baseline
d) skin biopsy with a negative pathology report
e) increases in pleural effusions present at baseline
f) skin lesions which were deemed not measurable because they were too small

Alternatively, the FDA also defined scenarios FULFILLING the definition of progressive disease:

a) radiation therapy to a lymph node
b) radiation therapy to a new pathologic fracture
c) new hydronephrosis with no other known etiology
d) new effusions which did not resolve
e) new lesions detected by follow up MRI but not by baseline CT

The FDA conducted a primary analysis of the data (Table 15) and then an additional analysis referred to as FDA data set (Table 16). For the primary analysis the FDA censored the data in the following fashion:

a) Patients who were enrolled but never treated for reasons not related to the severity of their disease were censored at the date of enrollment.
b) Patients who had not progressed and had not left the study were censored at the date of last assessment.
c) Patients who had left the study prior to determination of progression were censored at the date of the last assessment.

For the additional analysis, the FDA assigned the date of progressive disease using the following rules:

a) Date of progressive disease as determined by the REC in cases other than those described below or fulfilling the above noted criteria for progression.
b) Patients for whom a study discontinuation sheet was filled out and who died shortly thereafter, were censored at the date of their last assessment; if no assessment was performed they were assigned as having progressive disease at the date of their last therapy. (The date of death was used in survival analysis.)
c) Patients who were unable to be assess at a given time point due to lack of required information and for whom there were additional assessments at future time points, were assigned as having progressive disease at the date of the assessment which was lacking plus one day.
d) Patients who received non-protocol defined therapy were assigned as having progressive disease at the date of last assessment. (For the time to treatment failure analysis they were counted as treatment failures at the date that the non-protocol therapy was administered).

The results of both analyses, sponsor data set and FDA data set, demonstrated a significant improvement in time to progression with a log rank p value of < 0.001 in favor of Herceptin®; this benefit applied to both the pooled chemotherapy analyses (Herceptin® plus Chemo vs. Chemo alone) and the subgroup analyses (ACH vs. AC and TH vs. T). The time to progression was 1.9 months longer in the ACH group compared with the AC alone group and 4.2 months longer in the TH group compared with the T alone group.

We also evaluated those patients entered on study prior to the major protocol changes made in Amendment 2 (Am 2): some of these patients were allowed to be treated with paclitaxel (Amendment 1) but the study was still blinded and the patient selection criteria had not been broadened beyond the inclusion of patients with prior anthracycline therapy. There were 97 patients enrolled prior to Am 2 and of those, approximately 25% were treated with paclitaxel compared to the 40% ratio by the end of enrollment to the study. These data appear in Table 15 and are most appropriately compared to the AC subgroups. The absolute improvement in median time to progression appeared to be upheld even though the p value was 0.09 due to the smaller number of patients.

The time to progression data are presented below in Tables 15 and 16 and Figures 2, 3, and 4.

Table 15. Time to Progression - Sponsor derived data sets H0648g

Endpoint	AC + H	AC	T + H	T	*Chemo+H*	*Chemo*
Time to progression						
Median (months)	8.1	6.2	6.9	3.0	*7.6*	*4.6*
95% CI	(7.2, 9.9)	(5.1, 7.2)	(5.3, 9.9)	(2.1, 4.4)	*(6.9,9.5)*	*(4.4,5.5)*
Log rank test	p<0.001		p<0.001		*p<0.001*	
Hazard ratio	0.61 s.e. 0.14		0.38 s.e. 0.17		*0.51* *s.e. 0.11*	
Pts enrolled prior to AM2					*7.2* *(6.7, 9.5)*	*5.3* *(3.7, 6.5)*
Log rank					*p = 0.09*	
Hazard ratio					*0.69* *s.e. 0.23*	

Table 16. Time to Progression - FDA derived Data Sets H0648g.

Endpoint	AC + H	AC	T + H	T	*Chemo+H*	*Chemo*
Time to progression						
Median (months)	7.6	5.7	6.7	2.5	*7.2*	*4.5*
95% CI	(7.2, 9.4)	(4.6, 7.1)	(5.3, 9.9)	(2.0, 4.3)	*(6.9, 8.6)*	*(4.0, 4.8)*
Log rank test	p=0.001		p<0.0001		*p<0.0001*	
Hazard ratio	0.65 (0.47, 0.83)		0.39 (0.27, 0.53)		*0.51*	